

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 June 2003 (05.06.2003)

PCT

(10) International Publication Number
WO 03/045388 A1

- (51) International Patent Classification⁷: **A61K 31/46**, (74) Common Representative: **NEUROSEARCH A/S**,
A61P 9/10, 25/00, C07D 451/02, 471/18 Patent Department, 93 Pederstrupvej, DK-2750 Ballerup (DK).
- (21) International Application Number: **PCT/DK02/00796**
- (22) International Filing Date:
28 November 2002 (28.11.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
PA 2001 01781 30 November 2001 (30.11.2001) DK
- (71) Applicant (for all designated States except US): **NEUROSEARCH A/S** [DK/DK]; 93 Pederstrupvej, DK-2750 Ballerup (DK).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **SCHEEL-KRÜGER, Jørgen** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). **RØNN, Lars, Christian, B.** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 03/045388 A1

(54) Title: TROPANE DERIVATIVES HAVING DOPAMINE REUPTAKE INHIBITOR ACTIVITY FOR THE TREATMENT OF ISCHEMIC DISEASES

(57) Abstract: The present invention relates to the use of tropane derivatives having dopamine reuptake inhibitor activity for the treatment of diseases associated with reduced blood flow to the brain or with instances of a temporary break in blood supply to the brain, such as ischemic diseases.

TROPANE DERIVATIVES HAVING DOPAMINE REUPTAKE INHIBITOR ACTIVITY FOR THE TREATMENT OF ISCHEMIC DISEASES

TECHNICAL FIELD

5 The present invention relates to the use of tropane derivatives having dopamine reuptake inhibitor activity for the treatment of diseases associated with reduced blood flow to the brain or with instances of a temporary break in blood supply to the brain, such as ischemic diseases.

BACKGROUND ART

10 Cerebral ischemia can result in varying degrees of tissue damage. Conditions of severe ischemia can produce irreversible injury, whereas in conditions of moderate ischemia, tissue damage may be reversible. The reversibility of tissue damage – i.a. in the striatum – is important for the development of new therapeutic approaches for treatment.

15 In connection with an incidence of cerebral ischemia, an excessive amount of glutamate is released from the cortex to the striatum resulting in an excessive depolarization of dopaminergic nerve terminals primarily mediated by sodium influx. This depolarization results in a massive efflux of dopamine, which in turn exerts a neurodegenerative effect in the striatum.

20 Compounds capable of reducing the striatal dopamine level in such situations would therefore be considered useful for the treatment of diseases associated with reduced blood flow to the brain or with instances of a temporary break in blood supply to the brain, such as ischemic diseases.

25 It has been mentioned that dopamine release mediated by reversal of the dopamine transporter (DAT) may also be of importance in ischemic conditions in the striatum such that a part of the neurodegenerative changes in the striatum following ischemia results from dopamine release mediated by the dopamine transporter (Leviel V, Neurochemistry International, 38, 83-106, 2001).

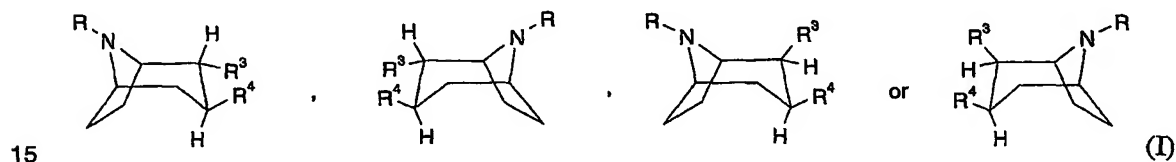
DETAILED DISCLOSURE OF THE INVENTION

35 It has now been found that a tropane derivative having dopamine reuptake inhibitor activity is useful in the treatment, prevention or alleviation of a disease associated with reduced blood flow to the brain or with an instance of a temporary break in blood supply to the brain.

Thus, in a first aspect the invention provides the use of a tropane derivative having dopamine reuptake inhibitor activity or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment, prevention or alleviation of a disease associated with reduced blood flow to the brain or with an instance of a temporary break in blood supply to the brain.

In a second aspect, the invention provides a method for the treatment, prevention or alleviation of a disease associated with reduced blood to the brain or with an instance of a temporary break in blood supply to the brain in a subject, comprising administering to said subject a therapeutically effective amount of a tropane derivative having dopamine reuptake inhibitor activity or a pharmaceutically acceptable salt thereof.

In one embodiment, the tropane derivative having dopamine reuptake inhibitor activity is a compound of the general formula (I)



or a pharmaceutically acceptable addition salt thereof or the N-oxide thereof, wherein

R is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl or 2-hydroxyethyl;

R³ is

- 20
- **CH₂-X-R'**,
 wherein X is O, S, or NR'';
 wherein R'' is hydrogen or alkyl; and
 R' is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or -CO-alkyl;
 - **heteroaryl** which may be substituted one or more times with
- 25
- alkyl, cycloalkyl, or cycloalkylalkyl;
 - phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
 - phenylphenyl;
- 30
- pyridyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
 - thienyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or
- 35

- benzyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or
- $(\text{CH}_2)_n\text{CO}_2\text{R}^{11}$, COR^{11} , or CH_2R^{12} ;
5 wherein R^{11} is
 - alkyl, cycloalkyl, or cycloalkylalkyl;
 - phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
 - 10 ○ phenylphenyl;
 - pyridyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
 - thienyl which may be substituted one or more times with substituents
15 selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or
 - benzyl;

n is 0 or 1; and
 R^{12} is

 - 20 ○ O-phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or
 - O-CO-phenyl which may be substituted one or more times with
25 substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or- $\text{CH}=\text{NOR}'$;
wherein R' is
 - hydrogen;
 - alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl or aryl; all of which may
30 be substituted with
 - $-\text{COOH}$;
 - $-\text{COO-alkyl}$;
 - $-\text{COO-cycloalkyl}$; or
 - phenyl which may be substituted one or more times with
35 substituents selected from the group consisting of halogen, CF_3 , CN, alkyl, cycloalkyl, alkoxy, cycloalkoxy, alkenyl, alkynyl, amino, and nitro;

R⁴ is

- **3,4-methylenedioxyphenyl or**
- **phenyl, benzyl, naphthyl, or heteroaryl** all of which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, cycloalkoxy, alkyl, cycloalkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl.

In a special embodiment of the compound of general formula I, R³ is

- **1,2,4-oxadiazol-3-yl** which may be substituted in the 5 position with
 - alkyl, cycloalkyl, or cycloalkylalkyl;
 - phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
 - phenylphenyl; or
 - benzyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or
- **1,2,4-oxadiazol-5-yl** which may be substituted in the 3 position with
 - alkyl, cycloalkyl, or cycloalkylalkyl;
 - phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
 - phenylphenyl;
 - benzyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
 - pyridyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro and heteroaryl; or
 - thienyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro and heteroaryl.

In a further special embodiment of the compound of general formula I, R³ is

- **CH₂-X-R'**,
wherein X is O, S, or NR'';
wherein R'' is hydrogen or alkyl; and
R' is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or -CO-alkyl.

In a still further embodiment of the compound of general formula I, R³ is

- **CH=NOR'**;

wherein R' is

- hydrogen;
- alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl or aryl; all of which may be substituted with
 - -COOH;
 - -COO-alkyl;
 - -COO-cycloalkyl; or
 - phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkyl, cycloalkyl, alkoxy, cycloalkoxy, alkenyl, alkynyl, amino, and nitro.

In a further special embodiment of the compound of general formula I, R⁴ is phenyl, which is substituted once or twice with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, cycloalkoxy, alkyl, cycloalkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl.

In a more special embodiment, R⁴ is phenyl substituted once or twice with chlorine.

In a further special embodiment, the tropane derivative having dopamine reuptake inhibitor activity is a (1R,2R,3S)-2,3-disubstituted tropane derivative of formula I.

In a still further embodiment, the tropane derivative having dopamine reuptake inhibitory activity is a compound of general formula I wherein R³ is

- -CH₂-X-R', wherein X is O or S, and R' is methyl, ethyl, propyl, or cyclopropylmethyl;
 - **CH=NOR'**;
- wherein R' is hydrogen or alkyl, or
- **1,2,4-oxadiazol-5-yl** which may be substituted in the 3 position with alkyl.

In a still further embodiment, the tropane derivative having dopamine reuptake inhibitory activity is a compound of general formula I wherein R is hydrogen, methyl, ethyl or propyl.

In a still further embodiment, the tropane derivative having dopamine reuptake inhibitory activity is a compound of general formula I wherein R⁴ is 3,4-dichlorophenyl.

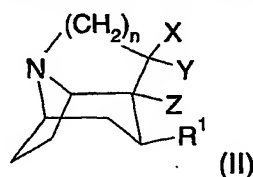
In a special embodiment, the tropane derivative having dopamine reuptake inhibitor activity is a compound of the general formula (I) selected from:

- (1R,2R,3S)-2-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)tropane;
- (1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)tropane;
- 5 (1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(4-methylphenyl)-tropane;
- (1R,2R,3S)-2-(3-Benzyl-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)tropane;
- (1R,2R,3S)-2-(3-(4-Phenyl-phenyl)-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)tropane;
- (1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(2-naphthyl)tropane;
- (1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-aldoxime;
- 10 (1R,2R,3S)-3-(3,4-Dichlorophenyl)-tropane-2-O-methyl-aldoxime;
- (1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-benzyl-aldoxime;
- (1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-ethoxycarbonylmethyl-aldoxime;
- (1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-methoxycarbonylmethyl-aldoxime;
- (1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(1-ethoxycarbonyl-1,1-dimethyl-
- 15 methyl)-aldoxime;
- (1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-carboxymethyl-2-aldoxime;
- (1R,2R,3S)-N-Normethyl-3-(3,4-dichlorophenyl)tropane-2-O-methyl-aldoxime;
- (1R,2R,3S)-N-Normethyl-3-(3,4-dichlorophenyl)tropane-2-O-benzyl-aldoxime;
- (1R,2R,3S)-3-(4-Methylphenyl)tropane-2-O-methyl-aldoxime;
- 20 (1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(1,1-dimethylethyl)-aldoxime;
- (1R,2R,3S)-3-(4-Chlorophenyl)tropane-2-O-aldoxime;
- (1R,2R,3S)-3-(4-Chlorophenyl)tropane-2-O-methylaldoxime hydrochloride;
- (1R,2R,3S)-3-(4-Chlorophenyl)tropane-2-O-methoxycarbonylmethyl-aldoxime;
- (1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(2-propynyl)-aldoxime;
- 25 (1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(2-methylpropyl)-aldoxime;
- (1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-cyclopropylmethyl-aldoxime;
- (1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-ethyl-aldoxime;
- (1R,2R,3S)-2-Methoxymethyl-3-(3,4-dichlorophenyl)-tropane;
- (1R,2R,3S)-2-Isopropoxymethyl-3-(3,4-dichlorophenyl)-tropane;
- 30 (1R,2R,3S)-2-Ethoxymethyl-3-(3,4-dichlorophenyl)-tropane;
- (1R,2R,3S)-2-Cyclopropylmethyloxymethyl-3-(3,4-dichlorophenyl)-tropane;
- (1R,2R,3S)-2-Methoxymethyl-3-(4-chlorophenyl)-tropane;
- (1R,2R,3S)-N-Normethyl-2-methoxymethyl-3-(4-chlorophenyl)-tropane;
- (1R,2R,3S)-2-Ethoxymethyl-3-(4-chlorophenyl)-tropane;
- 35 (1R,2R,3S)-N-Normethyl-2-methoxymethyl-3-(3,4-dichlorophenyl)-tropane;
- (1R,2R,3S)-N-Normethyl-2-ethoxymethyl-3-(3,4-dichlorophenyl)-tropane;
- (1R,2R,3S)-N-Normethyl-2-ethoxymethyl-3-(4-chlorophenyl)-tropane;
- (1R,2R,3S)-N-Normethyl-2-cyclopropylmethyloxymethyl-3-(4-chlorophenyl)-tropane;

- (1R,2R,3S)-2-Cyclopropylmethyloxymethyl-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-Ethylthiomethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-Hydroxymethyl-3-(4-fluorophenyl)tropane;
(1R,2R,3S)-2-Hydroxymethyl-3-(3,4-dichlorophenyl)tropane;
5 (1R,2R,3S)-N-Normethyl-N-(*tert*-butoxycarbonyl)-2-hydroxymethyl-3-(3,4-dichlorophenyl)tropane;
(1R,2R,3S)-2-Hydroxymethyl-3-(4-chlorophenyl)tropane;
(1R,2R,3S)-2-(3-(2-Furanyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(3-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
10 (1R,2R,3S)-N-Normethyl-N-allyl-2-(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-N-ethyl-2-(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-N-(2-hydroxyethyl)-2-(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)-3-
15 (3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-2-(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-N-allyl-2-(3-(3-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
20 (1R,2R,3S)-N-Normethyl-N-allyl-2-(3-(2-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(2-Thienyl)-1,2,4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(2-Thienyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(4-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
25 (1R,2R,3S)-2-(3-(2-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(4-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(3-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(2-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)-tropane;
30 (1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(4-methylphenyl)-tropane;
(1R,2R,3S)-2-(3-Benzyl-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)-tropane;
(1R,2R,3S)-2-(3-(4-Phenylphenyl)-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)-tropane;
(1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(2-naphthyl)-tropane;
(1R,2R,3S)-2-(4-Chlorophenoxy-methyl)-3-(4-fluorophenyl)-tropane;
35 (1R,2R,3S)-2-(4-Chlorophenoxy-methyl)-3-(4-fluorophenyl)-tropane;
(1R,2R,3S)-2-(4-Chlorophenoxy-methyl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(4-Chlorophenoxy-methyl)-3-(4-methylphenyl)-tropane;
(1R,2R,3S)-2-(4-Benzoyloxy-methyl)-3-(4-fluorophenyl)-tropane;

- (1R,2R,3S)-2-Carbomethoxy-3-(2-naphthyl)-tropane;
 (1R,2R,3S)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-tropane;
 (1R,2R,3S)-2-Carbomethoxy-3-benzyl-tropane;
 (1R,2R,3S)-2-Carbomethoxy-3-(4-chlorophenyl)-tropane;
 5 (1R,2R,3S)-2-Carbomethoxy-3-(4-methylphenyl)-tropane;
 (1R,2R,3S)-2-Carbomethoxy-3-(1-naphthyl)-tropane;
 (1R,2R,3S)-2-Carbomethoxy-3-(4-phenylphenyl)-tropane;
 (1R,2R,3S)-2-Carbomethoxy-3-(4-*t*-butyl-phenyl)-tropane;
 (1R,2R,3S)-2-(4-Fluoro-benzoyl)-3-(4-fluorophenyl)-tropane;
 10 or a pharmaceutically acceptable addition salt thereof.

In one embodiment, the tropane derivative having dopamine reuptake inhibitor activity is a compound of the general formula (II)



15

or any of its enantiomers or any mixture thereof, a pharmaceutically acceptable addition salt thereof or the N-oxide thereof
 wherein

- X and Y together forms =O, =S, =NOR², =CR³R⁴, =N-CN, =N-NR⁷R⁸, -(CH₂)_m-, or
 20 -W'-(CH₂)_p-W''-, or one of X and Y is hydrogen and the other is -OR⁵, -SR⁵, or -NR⁵R⁶
 Z is hydrogen, -COOR⁹;
 R³ and R⁴ are independently hydrogen, halogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, aryl, arylalkyl, or -(CH₂)_q-COOR²;
 R², R⁵ and R⁶ are independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl,
 25 alkynyl, aryl, or arylalkyl, -CO-alkyl, or -SO₂-alkyl;
 R⁷ and R⁸ are independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, or arylalkyl;
 R⁹ is alkyl, alkenyl or alkynyl;
 R¹ is alkyl, alkenyl, alkynyl, aryl, or arylalkyl;
 30 where said aryl groups may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, cycloalkoxy, alkyl, cycloalkyl, alkenyl, alkynyl, amino, alkylamino, dialkylamino and nitro;
 W' and W'' are each independently O or S;
 n is 1, 2, 3, or 4;
 35 m is 2, 3, 4, or 5;
 p is 1, 2, 3, 4, or 5; and
 q is 0, 1, 2, 3, or 4.

In a special embodiment, the tropane derivative having dopamine reuptake inhibitor activity is a compound of the general formula (II) selected from:

- (1S,2S,4S,7R)-2-(3,4-Dichlorophenyl)-8-azatricyclo[5.4.0.0^{4,8}]undecan-11-one;
- (1S,2S,4S,7R)-2-(3,4-Dichlorophenyl)-8-azatricyclo[5.4.0.0^{4,8}]undecan-11-ol;
- 5 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one;
- (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one O-methyl-oxime;
- (1S,2S,4S,7R)-2-(4-Chlorophenyl)-8-azatricyclo[5.4.0.0^{4,8}]undecan-11-one;
- (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-ol;
- 10 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-yl acetate;
- (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-yl methane sulphate;
- (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-5-methoxy-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one;
- (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-5-ethoxy-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one;
- 15 (1S,3S,4S,8R)-3-(4-Chlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one;
- (1S,3S,4S,8R)-3-(4-Chlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-ol;
- (1S,3S,4S,8R)-3-(4-Chlorophenyl)-5-ethoxy-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one;
- (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one O-benzyl-oxime;
- 20 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one O-allyl-oxime;
- (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one oxime;
- (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one O-tert-butyl-oxime;
- 25 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one O-ethyl-oxime;
- (1S,3S,4S,8R)-5-Allyloxy-3-(3,4-dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one;
- Ethyl (1S,3S,4S,8R)-2-[3-(3,4-dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-yliden]acetate;
- 30 (1S,3S,4S,8R)-3-(4-Chlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one oxime;
- N1-[1S,3S,4S,8R)-3-(4-Chlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-yl]acetamide;
- (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-yl amine;
- or a pharmaceutically acceptable addition salt thereof.

- 35 In one further embodiment, the disease to be treated, prevented or alleviated is selected from ischemic diseases, anoxic episodes, and injury to the brain and other parts of the CNS caused by trauma or other injury, for example a blow to the head. In such reduced blood flow episodes, or episodes where there is a temporary break in blood supply, oxygen supply to the brain is reduced or interrupted.

In a further embodiment, the disease to be treated, prevented or alleviated is selected from cerebrovascular disorders such as cerebral ischemia or cerebral infarction resulting from a range of conditions, such as tromboembolic or haemorrhagic stroke, cerebral vasospasm, hypoglycaemia, cardiac arrest, perinatal asphyxia, anoxia such as from near-drowning, pulmonary surgery and cerebral trauma.

The method can be used in the treatment or prevention of traumatic brain injury, in particular ischemic, hypoxic or anoxic brain damage, spinal cord injury, tissue ischemia and reperfusion injury in a mammal at risk for such damage.

10 The brain damage may brain damage may follow or be caused by: cerebral ischemia, cardiac arrest, high-risk surgery such as cardiac surgery, stroke, neonatal hypoxia, hypoxia caused by compromised lung function, neonatal anoxia, anoxia caused by compromised lung function, cerebral trauma, secondary regional ischemia induced by brain oedema, increased intercranial pressure, open brain surgery, 15 endarterectomy, surgical interventions involving temporary, artificially sustained arrest of cardiopulmonary functions resulting in impairment of cerebral blood flow, and emergency treatment involving cardiopulmonary resuscitation (CPR).

In a special embodiment, the disease to be treated, prevented or alleviated is acute treatment of ischemic stroke, treatment of brain damage following global 20 cerebral ischemia, or prevention of brain damage following high risk surgery.

In many instances of brain ischemia, treatment is not available to the patient for several, e.g. up to 6 hours, in stroke patients typically 3 to 6 hours, after the ischemic injury. Such a delay places great demands on any therapeutic regime designed to mitigate ischemic brain injury. It has been found, however, that the 25 tropane derivative having dopamine reuptake inhibitor activity for use according to the invention is surprisingly effective whether administered pre-ischemically or post-ischemically.

When administered post-ischemically it is advisable that the tropane derivative having dopamine reuptake inhibitor activity be administered within one day 30 of the ischemic insult. Although the tropane derivative having dopamine reuptake inhibitor activity used in the invention may be administered as late as 14 hours after brain reperfusion, the treatment should preferably be carried out within 12 hours of ischemic alleviation or reperfusion. Preferably, the treatment should occur within 6 hours of alleviation of ischemia. Yet more preferred is the administration of the tropane 35 derivative having dopamine reuptake inhibitor activity used in the invention within 3 hours of alleviation of ischemia

As used herein, CNS includes the brain and spinal cord and combating includes both therapy and diagnosis.

Tropane derivatives having dopamine reuptake inhibitor activity

The potential of a given substance to act as a dopamine reuptake inhibitors activity may be determined using standard *in vitro* binding assays and/or standard *in vivo* functionality tests, such as those described in "Test methods".

The tropane derivative having dopamine reuptake inhibitor activity for use according to the invention may in particular be tropane derivatives such as those disclosed the NeuroSearch patent applications EP 604355, EP 604352, US 5444070, EP 604354, WO 95/28401, and WO 97/30997, and fused tropane derivatives such as those disclosed NeuroSearch application WO 97/16451.

In one embodiment, the tropane derivative having dopamine reuptake inhibitor activity shows an IC_{50} value of less than 1 μ M, preferably less than 100 nM, more preferably less than 50 nM, and even more preferably less than 10 nM when tested for *in vitro* inhibition of 3H -DA uptake (test method 1).

In a second embodiment, the tropane derivative having dopamine reuptake inhibitor activity shows an ED_{50} value of less than 500 mg/kg, preferably less than 100 mg/kg, more preferably less than 50 mg/kg, more preferably less than 20 mg/kg, and even more preferably less than 10 mg/kg when tested for *in vivo* inhibition of 3H -WIN 35428 binding p.o., s.c. or i.p. (test method 5).

In a further embodiment, the tropane derivative having dopamine reuptake inhibitor activity shows a protection against MPTP of more than 60%, preferably more than 70%, and even more preferably more than 80% at 20 mg/kg of the test substance when tested for effect on striatal dopamine in mice treated with MPTP (test method 8). In a still further embodiment, the tropane derivative having dopamine reuptake inhibitor activity shows a protection against MPTP of more than 60%, preferably more than 70%, and even more preferably more than 80% at 10 mg/kg of the test substance when tested for effect on striatal dopamine in mice treated with MPTP.

The above examples of tropane derivative having dopamine reuptake inhibitor activity are not intended to be in any way limiting to the scope of the invention as claimed.

Definition of Substituents

In the context of this invention alkyl designates a straight chain or a branched chain containing of from one to six carbon atoms (C_1 - C_6 alkyl), including but not limited to methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl. In a preferred embodiment of this invention alkyl represents a C_1 - C_4 alkyl, preferably a C_1 - C_3 alkyl, most preferred methyl, ethyl, propyl or isopropyl.

In the context of this invention cycloalkyl designates a cyclic alkyl containing of from three to seven carbon atoms (C_3 - C_7 cycloalkyl), including but not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

In the context of this invention alkenyl designates a group containing of from
5 two to six carbon atoms (C_2 - C_6 alkenyl), including at least one double bond, for example, but not limited to ethenyl, 1,2- or 2,3-propenyl, 1,2-, 2,3-, or 3,4-butenyl.

In the context of this invention alkynyl designates a group containing of from two to six carbon atoms (C_2 - C_6 alkynyl), including at least one triple bond, for example, but not limited to ethynyl, 1,2- or 2,3-propynyl, 1,2-, 2,3- or 3,4-butyne.

10 In the context of this invention cycloalkyl-alkyl designates a cycloalkyl as defined above which is attached to an alkyl as also defined above, e.g. cyclopropylmethyl.

In the context of this invention aryl designates an aromatic hydrocarbon, such as phenyl or naphthyl.

15 In the context of this invention alkoxy designates an alkyl-O-, where alkyl is as defined above.

In the context of this invention acyl designates an alkyl-CO-, where alkyl is as defined above.

20 In the context of this invention halogen designates a fluorine, a chlorine, a bromine or an iodine atom.

In the context of this invention amino represents NH_2 , NH-alkyl, or N-(alkyl)₂, wherein alkyl is as defined above.

In the context of this invention heteroaryl designates a 5- or 6-membered heterocyclic monocyclic group, for example, but not limited to, oxazol-2-yl, oxazol-4-yl,
25 oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-oxadiazol-3-yl, 1,2,5-oxadiazol-4-yl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-4-yl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-
30 pyridyl.

Steric Isomers

The chemical compounds for use in the invention may exist in (+) and (-) forms as well as in racemic forms. The use of racemates of these isomers and the
35 individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical

antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphor-sulphonate) salts for example.

5 The chemical compounds for use in the invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of
10 the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Moreover, some of the chemical compounds for use in the invention may
15 thus exist in two forms, syn- and anti-form (Z- and E-form), depending on the arrangement of the substituents around a $-C=C-$ or $-C=N-$ double bond. A chemical compound for use according to the present invention may thus be the syn- or the anti-form (Z- and E-form), or it may be a mixture hereof.

20 **Pharmaceutically Acceptable Salts**

The tropane derivative having dopamine reuptake inhibitor activity for use according to the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound for use
25 according to the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate,
30 the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and
35 described in the art.

Metal salts of a chemical compound for use according to the invention include alkali metal salts such as the sodium salt of the chemical compound containing a carboxy group.

The term "prodrug" denotes a compound, which is a drug precursor and which, following administration and absorption, release the drug in vivo via some metabolic process.

Particularly favoured prodrugs are those that increase the bioavailability of the compounds for use according to the invention (e.g. by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a specific biological compartment (e.g. the brain or lymphatic system).

Thus examples of suitable prodrugs of the substances according to the invention include compounds modified at one or more reactive or derivatizable groups of the parent compound. Of particular interest are compounds modified at a carboxyl group, a hydroxyl group, or an amino group. Examples of suitable derivatives are esters or amides.

15 **Pharmaceutical Compositions**

The invention provides the use of pharmaceutical compositions comprising a therapeutically effective amount of the dopamine reuptake inhibitor. While a tropane derivative having dopamine reuptake inhibitor activity for use in therapy according to the invention may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the tropane derivative having dopamine reuptake inhibitor activity, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being
5 treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from
10 about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 $\mu\text{g/kg}$ i.v. and 1 $\mu\text{g/kg}$ p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1
15 $\mu\text{g/kg}$ to about 10 mg/kg/day i.v., and from about 1 $\mu\text{g/kg}$ to about 100 mg/kg/day p.o.

Combined treatment

The pharmaceutical composition for use according to the invention may include or may be used or administered in combination with one or more additional
20 drugs useful for the treatment, prevention or alleviation of a disease associated with reduced blood flow to the brain or with an instance of a temporary break in blood supply to the brain. Such additional drugs include compounds capable of blocking excitatory amino acid receptors (glutamate and aspartate) and neurotrophic compounds

25 Examples of compounds capable of blocking excitatory amino acid receptors include those substances described in the patent applications WO 94/26747, WO 96/08494, WO 96/08495, WO 98/14447 and WO 99/49864 (all NeuroSearch).

In the context of this invention, compounds with neurotrophic activity are
30 compounds that mimic or enhance the function of one or more endogenous neurotrophic factors. In one embodiment, a compound with neurotrophic activity is a compound that mimics or enhances the function of NGF, BDNF, and/or GDNF. In a further embodiment, a compound with neurotrophic activity is a compound that mimics or enhances the function of bFGF and/or EGF. In a special embodiment, a compound
35 with neurotrophic activity is a compound that mimics or enhances the function of NGF. The neurotrophic activity has not been ascribed to a specific step in the interaction between the growth factor and its receptor or in the growth factor signal transduction pathway. The potential of a given substance to act as a compound with neurotrophic

activity may be determined using standard *in vitro* binding assays and/or standard *in vivo* functional tests.

Compounds with neurotrophic activity include those substances described in the patent applications WO 98/07705 (Takeda Chem Ind Ltd), WO 00/34262 (Takeda Chem Ind Ltd), WO 00/32197 (Alcon Lab Inc), WO 97/40035 (NeuroSearch),
5 WO 00/43397 (NeuroSearch), international application WO 01/55110 (NeuroSearch), JP 2000226388-A (Takeda Chem Ind Ltd), WO 00/32197 (Alcon Lab), and WO 00/46222 (Schering AG).

Further examples of compounds with neurotrophic activity according to the
10 invention include 1-(1,3-benzodioxol-5-yl)-7,8,9,10-tetrahydro-1,3-benzodioxol[4,5-g]isoquinolin-7-one (Takeda), 2-(2,2,4,6,7-Pentamethyl-3-phenyl-2,3-dihydro-1-benzofuran-5-yl)-isoindoline (Takeda), 4-Aryl-1-phenylalkyl-1,2,3,6-tetrahydropyridine (Sanofi-Synthelabo), SR-57746A or 1-(2-napht-2-yl)ethyl-4-(3-trifluoromethylphenyl)-1,2,5,6-tetrahydropyridine (Sanofi-Synthelabo), AIT-082 (NeoTherapeutics), NIL-A
15 (Amgen Inc), K-252a (Cephalon), CEP-1347, GPI-1046 (Guilford), CTQ3, CTQ5 and CTQ8 (Centre de Neurochimie du CNRS), V-10,367 and V-13,661 (Vertex Pharmaceuticals Inc), ABS-205 (American Biogenic Sciences), Dexanabinol or HU-211 (Pharmos), or salts, free bases, racemates or enantiomers thereof.

The above examples of compounds capable of blocking excitatory amino
20 acid receptors and compounds with neurotrophic activity are not intended to be in any way limiting to the scope of the invention.

Methods of Preparation

The compounds of general formula (I) and (II) for use in the invention may
25 be prepared by conventional methods of chemical synthesis, e.g. those described in the NeuroSearch patent publications EP 604355, EP 604352, US 5444070, EP 604354, WO 97/30997, WO 95/28401, and WO 97/16451.

The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially
30 available chemicals.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Any possible combination of two or more of the embodiments described in
35 this patent application is comprised within the scope of the present invention.

The invention is further illustrated with reference to the following test methods and examples which are not intended to be in any way limiting to the scope of the invention as claimed.

TEST METHODS

Method 1

***In vitro* inhibition of ^3H -dopamine (^3H -DA) uptake in striatal synaptosomes**

5 In this test, the ability of dopamine reuptake inhibitor (below: the test compound) to inhibit the uptake of ^3H -dopamine in striatal synaptosomes is assessed.

Tissue preparations: Preparations are performed at 0-4°C unless otherwise indicated. Corpi striati from male Wistar rats (150-200 g) are homogenised for 5-10 sec in 100 volumes of ice-cold 0.32M sucrose containing 1 mM pargyline using an
10 Ultra-Turrax homogenizer. Monoamine oxidase activity will be inhibited in the presence of pargyline. The homogenate is centrifuged at 1000 x g for 10 min. The resulting supernatant is then centrifuged at 27,000 x g for 50 min and the supernatant is discarded. The pellet (P₂) is resuspended in oxygenated (equilibrated with an atmosphere of 96% O₂: 4% CO₂ for at least 30 min) Krebs-Ringer incubation buffer
15 (8000 ml per g of original tissue) at pH 7.2 containing 122 mM NaCl, 0.16 mM EDTA, 4.8 mM KCl, 12.7 mM Na₂HPO₄, 3.0 mM NaH₂PO₄, 1.2 mM MgSO₄, 1 mM CaCl₂, 10 mM glucose and 1 mM ascorbic acid.

Assay: Aliquots of 4.0 ml tissue suspension are added to 100 µl of test solution and 100 µl of ^3H -DA (1 nM, final concentration), mixed and incubated for 25
20 min at 37°C. Non-specific uptake is determined using benztropine (10 µM, final concentration). After incubation the samples are poured directly onto Whatman GF/C glass fibre filters under suction. The filters are then washed three times with 5 ml of ice-cold 0.9% (w/v) NaCl solution. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific uptake is calculated
25 as the difference between total uptake and non-specific uptake.

25-75% inhibition of specific binding must be obtained, before calculation of an IC₅₀. The test value is given as IC₅₀ (the concentration (µM) of the test compound which inhibits the specific binding of ^3H -DA by 50%).

30 Method 2

Inhibition of DA uptake in rat brain synaptosomes

In this method the ability of test compounds to inhibit the activity of dopamine transporter proteins is measured *in vitro* by analyzing the synaptosomal uptake of [^3H]dopamine ([^3H]DA).

35 Tissue preparation: Preparations are performed at 0-4°C unless otherwise indicated. The striata from male Wistar rats (150-200 g) are homogenized for 5-10 sec in 100 volumes of ice-cold 0.32 M sucrose containing 1 mM pargyline using a motor driven teflon pestle in a glass homogenizing vessel. Monoamine oxidase activity is inhibited in the presence of pargyline. The homogenates are centrifuged at 1000 x g

for 10 min. The resulting supernatants are then centrifuged at 27,000 x g for 50 min. The supernatants are discarded and the pellets (P₂) are resuspended in oxygenated (equilibrated with an atmosphere of 96% O₂: 4% CO₂ for at least 30 min) Krebs-Ringer incubation buffer (pH 7.2) (8000 ml per g of original tissue for the [³H]DA assay) containing 122 mM NaCl, 0.16 mM EDTA, 4.8 mM KCl, 12.7 mM Na₂HPO₄, 3.0 mM NaH₂PO₄, 1.2 mM MgSO₄, 0.97 mM CaCl₂, 10 mM glucose and 1 mM ascorbic acid.

Uptake assays: Aliquots of 4.0 ml tissue suspension are added to 0.1 ml of test solution and 0.1 ml of [³H]DA (1 nM, final concentration), mixed and incubated for 25 min at 37°C. Non-specific uptake is determined in the presence of benztropine (1 μM, final concentration). After incubation the samples are poured directly onto Whatman GF/C glass fibre filters under suction. The filters are then washed three times with 5 ml of ice-cold 0.9% (w/v) NaCl solution. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting using a Tri-carb™ liquid scintillation analyzer (model 1600CA; Packard, USA) Specific uptake is calculated as the difference between total uptake and non-specific uptake.

Data analysis: The test value is given as an IC₅₀ (the concentration (μM) of the test substance which inhibits the specific uptake of [³H]ligand by 50%). Three concentrations are been used to determine the inhibition curves from which the IC₅₀ values are determined. If a full curve is not available a 25-75% inhibition of specific binding must be obtained, before calculation of an IC₅₀.

$$IC_{50} = (\text{applied test substance concentration, } \mu\text{M}) \times \frac{1}{\left(\frac{C_o}{C_x} - 1\right)}$$

where C_o is specific uptake in control assays and C_x is the specific uptake in the test assay. (The calculations assume normal mass-action kinetics).

Method 3

Inhibition of *in vitro* [³H]GBR 12935 binding to the dopamine transporter in rat striatal synaptosomes

In this method the ability of test compounds to inhibit the binding of GBR 12935 to the dopamine transporter in vitro is assessed.

Tissue preparation: Preparations are performed at 0-4°C unless otherwise indicated. Striata from male Wistar rats (150-200 g) are homogenized for 5-10 sec in 10 ml Tris-citrate buffer (50 mM, pH 7.1) using an Ultra-Turrax homogenizer. The suspension is centrifuged at 27,000 x g for 15 min. The supernatant is discarded and the pellet is resuspended in Tris-citrate buffer containing 120 mM NaCl and 4 mM MgCl₂ (7000 ml per g of original tissue) and used for binding assays.

Binding assays: Aliquots of 1.0 ml tissue suspension are added to 0.050 ml of test solution and 0.050 ml of [³H]GBR 12935 (0.5 nM, final concentration), mixed and incubated for 60 min at 2°C. Non-specific binding is determined using GBR 12909 (1 µM, final concentration).

5 After incubation 5 ml of ice-cold buffer is added to the samples and poured directly onto Whatman GF/C glass fiber filters (for the [³H]GBR 12935 assay the filters are presoaked in 0.1% PEI for at least 20 min) under suction and immediately washed with 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting using a Tri-carb liquid scintillation analyzer
10 (model 1600CA; Packard, USA). Specific binding is calculated as the difference between total binding and non-specific binding.

Data analysis: The test value is given as an IC₅₀ (the concentration (µM) of the test substance which inhibits the specific binding of [³H]ligand by 50%).

Five to nine concentrations are been used to determine the inhibition curves from
15 which the IC₅₀ values are determined. If a full curve is not available a 25-75% inhibition of specific binding must be obtained, before calculation of an IC₅₀.

$$IC_{50} = (\text{applied test substance concentration, } \mu\text{M}) \times \frac{1}{\left(\frac{C_o}{C_x} - 1\right)}$$

20 where C_o is specific binding in control assays and C_x is the specific binding in the test assay. (The calculations assume normal mass-action kinetics).

Method 4

Inhibition of *in vitro* [³H]WIN 35428 binding to the dopamine transporter in rat striatal synaptosomes

25

In this method the ability of test compounds to inhibit the binding of WIN 35428 to the dopamine transporter *in vitro* is assessed.

Tissue preparation: Striata from male Wistar rats (150-200 g) are homogenized for 5-10 sec in 10 ml NaH₂PO₄ (50 mM, pH 7.4) using an Ultra-Turrax
30 homogenizer. The suspension is centrifuged at 27,000 x g for 15 min. The supernatant is discarded and the pellet is resuspended in phosphate buffer (1000 ml per g of original tissue) and used for binding assays.

Binding assays: Aliquots of 0.5 ml tissue suspension are added to 0.025 ml of test solution and 0.025 ml of [³H]WIN 35428 (1 nM, final concentration), mixed and
35 incubated for 60 min at 2°C. Non-specific binding is determined using cocaine (30 µM, final concentration).

After incubation 5 ml of ice-cold buffer is added to the samples and poured directly onto Whatman GF/C glass fiber filters (for the [³H]GBR 12935 assay the filters are presoaked in 0.1% PEI for at least 20 min) under suction and immediately washed with 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting using a Tri-carb liquid scintillation analyzer (model 1600CA; Packard, USA). Specific binding is calculated as the difference between total binding and non-specific binding.

Data analysis: The test value is given as an IC₅₀ (the concentration (μM) of the test substance which inhibits the specific binding of [³H]ligand by 50%).

- Five to nine concentrations are been used to determine the inhibition curves from which the IC₅₀ values are determined. If a full curve is not available a 25-75% inhibition of specific binding must be obtained, before calculation of an IC₅₀.

$$IC_{50} = (\text{applied test substance concentration, } \mu\text{M}) \times \frac{1}{\left(\frac{C_0}{C_x} - 1\right)}$$

- where C₀ is specific binding in control assays and C_x is the specific binding in the test assay. (The calculations assume normal mass-action kinetics).

Method 5

Inhibition of *in vivo* [³H]WIN 35428 binding

- The test substance is administered to groups of three female NMRI mice (25 g) at specified time points, either i.v., i.p., s.c. or p.o. Forty-five min before decapitation the mice are injected i.v. via the tail vein with 2.0 μCi of [³H]WIN 35428 in 0.25 ml saline. At the time of decapitation the striata are rapidly dissected on ice. Each striatum is weighed and dissolved for 36 h with 1 ml of 2% sodium-laurylsulfate. Two ml of scintillation cocktail is added to the solubilized tissue, and the amount of radioactivity per mg of tissue is determined by conventional liquid scintillation counting using a Tri-carb™ liquid scintillation analyzer (model 1600CA; Packard, USA). Groups of vehicle treated mice serves as controls. To determine non-specific binding, groups of mice are injected with WIN 35428 (2.5 mg/kg i.p.; 0.75 ml) at the time of [³H]WIN 35428 injection. Specific binding is calculated as the difference between binding in vehicle and WIN 35428 treated mice.

Data analysis: The test value is given as an ED₅₀ (the dose (mg/kg) of the test substance which inhibits the specific binding of [³H]WIN 35428 by 50%).

- Three doses of test substance are used to determine the dose response curve from which the ED₅₀ value is determined. If a full curve is not available a 25-75% inhibition of specific binding must be obtained before calculation of an ED₅₀ value.

$$ED_{50} = (\text{administered test substance dose, mg/kg}) \times \frac{1}{\left(\frac{C_o}{C_x} - 1\right)}$$

where C_o is specific binding in controls and C_x is the specific binding in mice treated with test substance.

5

Method 6

Protection of the Hippocampus after Transient Global Ischaemia in Gerbils

In this experiment, the neuroprotective effect of a test compound is assessed in an animal model of transient global ischaemia.

10 Method: In halothane anaesthetised gerbils, right and left carotid arteries are located and occluded for 4 minutes. Animals are kept at normal body temperature before and after the operation using heating lamps. During surgery, the gerbils are placed on heating pads, the body temperature is controlled and maintained at $37 \pm 0.5^\circ\text{C}$. The test compound is dosed at specified time points after the ischaemic insult,
15 either i.v., i.p., s.c. or p.o.

Four days later, the animals are sacrificed, brains removed and cooled to -70°C . Thereafter, the brains are sectioned in $20 \mu\text{m}$ thick sections of which 5 - 7 with hippocampal tissue are selected and stained with hematoxylin-eosin.

The degree of hippocampal damage is categorised into one of four groups:

20

Group 1: no damage in the CA_1 -layer;

Group 2: the CA_1 -layer partly damaged;

Group 3: the CA_1 -layer completely damaged; and

Group 4: damage in more than just the CA_1 -layer.

The total ischaemia score is obtained as the sum of scores in the right- and
25 left hemisphere. Kendall's tau test was used for statistic evaluation.

Method 7

Protection of the Substantia Nigra after Transient Global Ischaemia in Gerbils

In this experiment, the neuroprotective effect of a test compound is
30 assessed in an animal model of transient global ischaemia.

Method: In halothane anaesthetised gerbils, right and left carotid arteries are located and occluded for 10 minutes. Animals are kept at normal body temperature before and after the operation using heating lamps. During surgery, the gerbils are placed on heating pads, the body temperature is controlled and maintained
35 at $37 \pm 0.5^\circ\text{C}$. The test compound is dosed at specified time points after the ischaemic insult, either i.v., i.p., s.c. or p.o.

Fourteen days later, the animals are sacrificed, brains removed and cooled to -70°C. Thereafter, the brains are sectioned in 20 µm thick sections through the substantia nigra region. Sections are stained for tyroxine hydroxylase (TH+) expression using immunohistochemistry. The number of TH+ cells in the sections is counted and the total number of TH+ cells in the substantia nigra is calculated by means of stereology.

Method 8

Transient Global Ischaemia in Gerbils

10 In this experiment, the neuroprotective effect of a test compound is assessed in an animal model of transient global ischaemia.

Method: In halothane anaesthetised gerbils, right and left carotid arteries are located and occluded for 4 minutes. Animals are kept at normal body temperature before and after the operation using heating lamps. During surgery, the gerbils are placed on heating pads, the body temperature is controlled and maintained at 37 ± 0.5°C. The test compound is dosed at specified time points after the ischaemic insult, either i.v., i.p., s.c. or p.o.

Four days later, the animals are sacrificed, brains removed and cooled to -70°C. Thereafter, the brains are sectioned in 20 µm thick sections of which 5 - 7 with hippocampal tissue are selected and stained with hematoxylin-eosin.

The degree of hippocampal damage is categorised into one of four groups:

Group 1: no damage in the CA₁-layer;

Group 2: the CA₁-layer partly damaged;

Group 3: the CA₁-layer completely damaged; and

25 Group 4: damage in more than just the CA₁-layer.

The total ischaemia score is obtained as the sum of scores in the right- and left hemisphere. Kendall's tau test was used for statistic evaluation.

Method 9

30 Mouse middle cerebral artery occlusion (MCAO)

In this experiment, the neuroprotective effect of a compound is assessed in an animal model of focal ischaemia.

Female NMRI-mice (27-38 g) are anaesthetized with halothane (2% halothane in 30% O₂-70% NO₂). During surgery the body temperature is maintained at 37 ± 0.5 °C by placing the mice on heating pads connected to a CMA/150 temperature controller. MCAO is performed as earlier described (Møller et al., Neurol Res, 17, 353-360, 1995). After MCAO, the mice are placed under heating lamps. The test compound is administrated at specified time points after the ischaemic insult, either i.v., i.p., s.c. or

p.o.. The control group is given vehicle. On the fourth day, the mice are sacrificed and the brains removed. The brains are frozen on dry ice and cut into 20 µm sections. Every 40th sections are sampled and the total infarct volume is used as the endpoint for ischemic damage. The infarct volume is estimated using the Cavalieri's volume estimator (Gundersen et al., AMPIS, 96, 379-394, 1998).

Method 10

Effect of a compound on striatal dopamine in mice treated with MPTP

In this test, the ability of compound to increase striatal dopamine in mice treated with MPTP is assessed.

Female C57BL/ 6J mice weighing 20-25 grams (Møllegaard Breeding and Research Centre) are adapted to the laboratory for 5-7 days before the experiments with food and water freely available, room temperature 22-24 °C. Light is on/off at 7 am and 6 pm, respectively. At least 5-8 mice are used per group. MPTP, HCL (RBI) is dissolved in saline just before the experiments and is tested in various doses 12.5, 25, 3x12.5 and 3x25 mg/kg sc. The test compound is tested following a pretreatment time between 30 min and 3 hrs before the subcutaneous sc injection of MPTP 25 mg/kg. The mice are sacrificed 48 hrs after the last dose of MPTP for the biochemical analysis of dopamine and its metabolites HVA and DOPAC. For biochemical analysis, the striatum of the mice is rapidly dissected out, frozen and stored at -80° C . On the day of analysis, one striatum per mouse (weighing 5-7 mg) is homogenised in 1 ml of 0.1 N Perchloric acid containing 5% EDTA . After centrifugation 14,000xG for 30 min. 200µl of the supernatant is filtered through a glass 0.22 µm filter. 20µl is then injected into our ESA Coulochem II HPLC equipment with a the following column (Caracholamine HR-80 4.6 mmX 80 mm 3µm Nucleosil C 18). The eluent is 10.25 g NaH₂ PO₄, 185 mg EDTA, 100 mg Octansulphonic acid. 9% methanol, pH 3.7, add 500 ml MilliQ water, filtered through 0.22 µm. The Colochem ESA analytical cell is 5014A and the ESA detector has the following settings: E₂ -175 mV, run time 16 min. for the elution of dopamine, DOPAC and HVA (DOPAC= 4.3 min; dopamine= 6.4 min and HVA = 12.7 min.). The autoinjector SHIMADZY sil-10A has the following settings; injection vol. 20 µl, 16 min analysis, temp 4°C. Flow rate from the pump is 0.80 ml/min. The analyses are calibrated with standards of 3 pM of dopamine, HVA and DOPAC for each 12 analysis run and are compared with our standard curves.

Method 11

Effect of a compound on extracellular dopamine measured by microdialysis

In this test, the ability of a compound to increase dopamine in various brain regions is assessed.

Male SPF Mol Wistar rats weighing 300-350 g are obtained from Møllegaard Breeding and Research Centre and housed in standard Macrolon cages sized 24x36x18 cm for at least 5 days under standard conditions at a temperature of $23 \pm 2^{\circ}\text{C}$ and a humidity of $60\% \pm 10\%$, and a 12 h light and dark cycle. The rats are housed in groups of two with food and water freely available ad libitum. For microdialysis, the rat is placed in a stereotaxic instrument under halothane anesthesia using 1½% halothane, 20% oxygen and 80% nitrous oxide. The rectal temperature is monitored and maintained at $37.0 \pm 1^{\circ}\text{C}$ during the experimental period using a heating pad (CMA 150 Carnegie Medicin). A small hole is drilled to allow a vertical probe (CMA/123), to be stereotaxically implanted into the right striatum, using the following coordinates relative to bregma : AP +1 mm; L 3 mm; DV -6 mm. The probes for the nucleus accumbens (CMA 122) is implanted vertical at the following coordinates: AP +2.4, L1.4 and DV -8mm. Similar experiments are performed with probes implanted into the nucleus accumbens in non anaesthetised freely moving animals. These experiments are performed 48 h after surgery during the daylight period in animals housed individually in plastic cages with food and water available ad libitum. In all cases, the injection sites are confirmed histologically according to the atlas of Paxinos and Watson.

After an initial 2h period, samples of dialysate are collected from halothane anaesthetised rats. The dosing of a test compound to these rats are usually initiated after the collection of 3 base line analyses. Dopamine and its metabolites are rapidly frozen to -18°C and then analyzed as soon as possible thereafter. The dialysis probe is perfused at a rate of 2 $\mu\text{l}/\text{min}$ (by a CMA/ 100 microperfusion pump) with Ringer's solution (147 mM NaCl, 4 mM KCl, 2.3 mM CaCl) i.e. Ringer's solution (NaCl 4.3 g, KCl 150 mg, CaCl_2 110.3 mg ad 500 ml) adjusted to pH 6.5 with 2 mM sodium phosphate buffer. The Ringer solution is filtered before use through Millipore glass filters (0.22 μm). The dialysate fractions (40 μl) are collected at 20 min intervals and then injected into the HPLC system. The concentration of dopamine (DA), dihydroxy phenyl acetic acid (DOPAC), homovanillic acid (HVA) and 5-hydroxy indolacetic acid (5-HIAA) are determined by high-performance liquid chromatography with electrochemical detection (HPLC-ED). The column is a reverse-phase liquid chromatography Catecholamine 3 μm ESA column at 23°C , the mobile phase consisting of 0.055 M sodium acetate with 0.1 nM octanesulfonic acid, 0.01 mM Na EDTA, and 10% methanol pH 3.7 adjusted with glacial acetic acid). The mobil phase is delivered by a HPLC pump (ESA) at 0.55 ml/min. Electrochemical detection is accomplished using an amperometric detector (Antec) with a glassy carbon electrode (0.8 V an Ag/AgCl reference) or a coulometric detector (Choulochem II model ESA; with a high sensitivity analytical cell (5011). (0,4V an Ag/AgCl reference).

Chromatograms are recorded by an integrator. The data are calculated as percent change of the basal concentration, the 100% value being defined as the average of the last 3 pretreatment values for each rat. The mean percentage values are then calculated for each 20 min sample for the rats in each group of treatment.

5

Method 12

Effect of a compound on turning behaviour after 6-OHDA lesion

In this test, the ability of a compound to influence the turning behaviour after a striatal or medial forebrain bundle and ventral tegmental area 6-OHDA lesion is assessed.

6-OHDA (20 µg free base dissolved in 0.9% NaCl supplemented with 0.02% ascorbic acid) is injected unilaterally in the striatum or in the medial forebrain bundle and the ventral tegmental area of halothane anaesthetised female Sprague Dawley rats weighing approximately 200-250 g with a glass capillary. Test compound or vehicle is administered i.p., p.o., s.c. or i.v. either daily or at specified time points starting after the 6-OHDA injection. The rotational behaviour of the 6-OHDA lesioned animals is monitored in automated rotometer bowls after administration of test compound alone or after administration of amphetamine (2.5 mg/kg i.p.), apomorphine (0.25 mg/kg s.c.), or L-dopa (2-10 mg/kg i.p.).

20

EXAMPLES

Example 1

Protection of the Substantia Nigra after Transient Global Ischaemia in Gerbils

Global forebrain ischemia was induced in Mongolian gerbils as described in test method 7 by occluding the common carotid arteries bilaterally for 10 min. The experiment was carried out for the following three groups of animals: 1) a control group (6 animals), 2) a group of animals subjected to carotid artery occlusion ischemia (6 animals) and 3) a group subjected to carotid artery occlusion ischemia and treatment with the test compound (8 animals). The animals of the control group were subjected to the same surgical procedure as group 2) except for the occlusion. The following test compound was used: (1R,2R,3S)-3-(3,4-dichlorophenyl)-tropane-2-O-methyl-aldoxime. The test compound was dosed 2 minutes after end of carotid artery occlusion at a concentration of 2 mg/kg i.p.

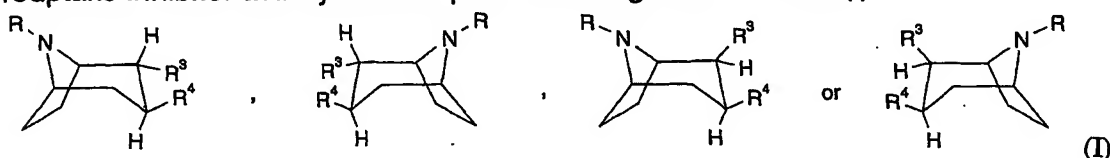
After 14 days, the animals were sacrificed and the brains sectioned. Sections comprising the substantia nigra were TH immunostained. The total number of TH positive cells after ischemia or in control animals were determined by means of stereological cell counting.

The results are shown in Table 1. In animals subjected to ischemia, the total number of TH positive cells in the substantia nigra (7510 \pm 1185) appeared to be lower than that in control animals (9531 \pm 653) indicating ischemia induced cell death in the substantia nigra. Surprisingly, the number of surviving TH positive cells in the substantia nigra after ischemia was apparently increased by treatment with the test compound indicating that this compound has a protective effect in ischemia.

Group	Mean number of cells	SEM (number of cells)
Control	9531	653
Ischemia	7510	1185
Ischemia + test compound	10615	1403

Claims

1. The use of a tropane derivative having dopamine reuptake inhibitor activity or a pharmaceutically acceptable salt thereof
- 5 for the manufacture of a medicament for the treatment, prevention or alleviation of a disease associated with reduced blood flow to the brain or with an instance of a temporary break in blood supply to the brain.
2. The use according to claim 1, wherein the tropane derivative having dopamine reuptake inhibitor activity is a compound of the general formula (I)



or a pharmaceutically acceptable addition salt thereof or the N-oxide thereof, wherein

R is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl or 2-hydroxyethyl;

15 R^3 is

- $\text{CH}_2\text{-X-R'}$,
wherein X is O, S, or NR'' ;
wherein R'' is hydrogen or alkyl; and
 R' is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or -CO-alkyl ;
- 20 • **heteroaryl** which may be substituted one or more times with
 - alkyl, cycloalkyl, or cycloalkylalkyl;
 - phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
 - 25 ○ phenylphenyl;
 - pyridyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
 - thienyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or
 - 30 ○ benzyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or
- 35 • $(\text{CH}_2)_n\text{CO}_2\text{R}^{11}$, COR^{11} , or CH_2R^{12} ;

wherein R^{11} is

- alkyl, cycloalkyl, or cycloalkylalkyl;
- phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
- phenylphenyl;
- pyridyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
- thienyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or
- benzyl;

n is 0 or 1; and

R^{12} is

- O-phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or
- O-CO-phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or

• **CH=NOR'**;

wherein R' is

- hydrogen;
- alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl or aryl; all of which may be substituted with
 - -COOH;
 - -COO-alkyl;
 - -COO-cycloalkyl; or
 - phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3 , CN, alkyl, cycloalkyl, alkoxy, cycloalkoxy, alkenyl, alkynyl, amino, and nitro;

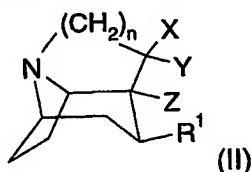
R^4 is

- **3,4-methylenedioxyphenyl or**
- **phenyl, benzyl, naphthyl, or heteroaryl** all of which may be substituted one or more times with substituents selected from the group consisting of halogen,

CF₃, CN, alkoxy, cycloalkoxy, alkyl, cycloalkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl.

3. The use according to claim 2, wherein R³ is
- 5 • **1,2,4-oxadiazol-3-yl** which may be substituted in the 5 position with
- alkyl, cycloalkyl, or cycloalkylalkyl;
 - phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
 - 10 ○ phenylphenyl; or
 - benzyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or
- **1,2,4-oxadiazol-5-yl** which may be substituted in the 3 position with
- 15 ○ alkyl, cycloalkyl, or cycloalkylalkyl;
 - phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
 - phenylphenyl;
 - 20 ○ benzyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;
 - pyridyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro and heteroaryl; or
 - 25 ○ thienyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF₃, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro and heteroaryl.
- 30 4. The use according to claim 2, wherein R³ is
- **-CH₂-X-R'**, wherein X is O or S, and R' is methyl, ethyl, propyl, or cyclopropylmethyl;
 - **CH=NOR'**;
 - 35 wherein R' is hydrogen or alkyl, or
 - **1,2,4-oxadiazol-5-yl** which may be substituted in the 3 position with alkyl.

5. The use according to claim 1, wherein the tropane derivative having dopamine reuptake inhibitor activity is a compound of the general formula (II)



- 5 or any of its enantiomers or any mixture thereof, a pharmaceutically acceptable addition salt thereof or the N-oxide thereof
wherein
X and Y together forms =O, =S, =NOR², =CR³R⁴, =N-CN, =N-NR⁷R⁸, -(CH₂)_m-, or
-W'-(CH₂)_p-W''-, or one of X and Y is hydrogen and the other is -OR⁵, -SR⁵, or -NR⁵R⁶
10 Z is hydrogen, -COOR⁹;
R³ and R⁴ are independently hydrogen, halogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, aryl, arylalkyl, or -(CH₂)_q-COOR²;
R², R⁵ and R⁶ are independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, or arylalkyl, -CO-alkyl, or -SO₂-alkyl;
15 R⁷ and R⁸ are independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, or arylalkyl;
R⁹ is alkyl, alkenyl or alkynyl;
R¹ is alkyl, alkenyl, alkynyl, aryl, or arylalkyl;
where said aryl groups may be substituted one or more times with substituents
20 selected from the group consisting of halogen, CF₃, CN, alkoxy, cycloalkoxy, alkyl, cycloalkyl, alkenyl, alkynyl, amino, alkylamino, dialkylamino and nitro;
W' and W'' are each independently O or S;
n is 1, 2, 3, or 4;
m is 2, 3, 4, or 5;
25 p is 1, 2, 3, 4, or 5; and
q is 0, 1, 2, 3, or 4.

6. The use according to claim 1, wherein the tropane derivative having dopamine reuptake inhibitor activity is selected from
30 (1R,2R,3S)-2-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)tropane;
(1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)tropane;
(1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(4-methylphenyl)tropane;
(1R,2R,3S)-2-(3-Benzyl-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)tropane;
(1R,2R,3S)-2-(3-(4-Phenyl-phenyl)-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)tropane;
35 (1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(2-naphthyl)tropane;

- (1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)-tropane-2-O-methyl-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-benzyl-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-ethoxycarbonylmethyl-aldoxime;
5 (1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-methoxycarbonylmethyl-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(1-ethoxycarbonyl-1,1-dimethyl-
methyl)-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-carboxymethyl-2-aldoxime;
(1R,2R,3S)-N-Normethyl-3-(3,4-dichlorophenyl)tropane-2-O-methyl-aldoxime;
10 (1R,2R,3S)-N-Normethyl-3-(3,4-dichlorophenyl)tropane-2-O-benzyl-aldoxime;
(1R,2R,3S)-3-(4-Methylphenyl)tropane-2-O-methyl-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(1,1-dimethylethyl)-aldoxime;
(1R,2R,3S)-3-(4-Chlorophenyl)tropane-2-O-aldoxime;
(1R,2R,3S)-3-(4-Chlorophenyl)tropane-2-O-methylaloxime hydrochloride;
15 (1R,2R,3S)-3-(4-Chlorophenyl)tropane-2-O-methoxycarbonylmethyl-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(2-propynyl)-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(2-methylpropyl)-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-cyclopropylmethyl-aldoxime;
(1R,2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-ethyl-aldoxime;
20 (1R,2R,3S)-2-Methoxymethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-Isopropoxymethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-Ethoxymethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-Cyclopropylmethyloxymethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-Methoxymethyl-3-(4-chlorophenyl)-tropane;
25 (1R,2R,3S)-N-Normethyl-2-methoxymethyl-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-Ethoxymethyl-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-2-methoxymethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-2-ethoxymethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-2-ethoxymethyl-3-(4-chlorophenyl)-tropane;
30 (1R,2R,3S)-N-Normethyl-2-cyclopropylmethyloxymethyl-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-Cyclopropylmethyloxymethyl-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-Ethylthiomethyl-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-Hydroxymethyl-3-(4-fluorophenyl)tropane;
(1R,2R,3S)-2-Hydroxymethyl-3-(3,4-dichlorophenyl)tropane;
35 (1R,2R,3S)-N-Normethyl-N-(*tert*-butoxycarbonyl)-2-hydroxymethyl-3-(3,4-
dichlorophenyl)tropane;
(1R,2R,3S)-2-Hydroxymethyl-3-(4-chlorophenyl)tropane;

- (1R,2R,3S)-2-(3-(2-Furanyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(3-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-N-allyl-2-(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
5 (1R,2R,3S)-N-Normethyl-N-ethyl-2-(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-N-(2-hydroxyethyl)-2-(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-2-(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-
10 tropane;
(1R,2R,3S)-N-Normethyl-N-allyl-2-(3-(3-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-N-Normethyl-N-allyl-2-(3-(2-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
15 (1R,2R,3S)-2-(3-(2-Thienyl)-1,2,4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(2-Thienyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(4-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(2-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(4-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;
20 (1R,2R,3S)-2-(3-(3-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-(3-(2-Pyridyl)-1,2,4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)-tropane;
(1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(4-methylphenyl)-tropane;
(1R,2R,3S)-2-(3-Benzyl-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)-tropane;
25 (1R,2R,3S)-2-(3-(4-Phenylphenyl)-1,2,4-oxadiazol-5-yl)-3-(4-fluorophenyl)-tropane;
(1R,2R,3S)-2-(3-Phenyl-1,2,4-oxadiazol-5-yl)-3-(2-naphthyl)-tropane;
(1R,2R,3S)-2-(4-Chlorophenoxy-methyl)-3-(4-fluorophenyl)-tropane;
(1R,2R,3S)-2-(4-Chlorophenoxy-methyl)-3-(4-fluorophenyl)-tropane;
(1R,2R,3S)-2-(4-Chlorophenoxy-methyl)-3-(3,4-dichlorophenyl)-tropane;
30 (1R,2R,3S)-2-(4-Chlorophenoxy-methyl)-3-(4-methylphenyl)-tropane;
(1R,2R,3S)-2-(4-Benzoyloxy-methyl)-3-(4-fluorophenyl)-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-(2-naphthyl)-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-benzyl-tropane;
35 (1R,2R,3S)-2-Carbomethoxy-3-(4-chlorophenyl)-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-(4-methylphenyl)-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-(1-naphthyl)-tropane;
(1R,2R,3S)-2-Carbomethoxy-3-(4-phenylphenyl)-tropane;

- (1R,2R,3S)-2-Carbomethoxy-3-(4-*t*-butyl-phenyl)-tropane;
 (1R,2R,3S)-2-(4-Fluoro-benzoyl)-3-(4-fluorophenyl)-tropane;
 (1S,2S,4S,7R)-2-(3,4-Dichlorophenyl)-8-azatricyclo[5.4.0.0^{4,8}]undecan-11-one;
 (1S,2S,4S,7R)-2-(3,4-Dichlorophenyl)-8-azatricyclo[5.4.0.0^{4,8}]undecan-11-ol;
 5 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one;
 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one O-methyl-oxime;
 (1S,2S,4S,7R)-2-(4-Chlorophenyl)-8-azatricyclo[5.4.0.0^{4,8}]undecan-11-one;
 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-ol;
 10 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]dec-5-yl acetate;
 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]dec-5-yl methane sulphate;
 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-5-methoxy-7-azatricyclo[5.3.0.0^{4,8}]decane;
 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-5-ethoxy-7-azatricyclo[5.3.0.0^{4,8}]decane;
 15 (1S,3S,4S,8R)-3-(4-chlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one;
 (1S,3S,4S,8R)-3-(4-chlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-ol;
 (1S,3S,4S,8R)-3-(4-Chlorophenyl)-5-ethoxy-7-azatricyclo[5.3.0.0^{4,8}]decane;
 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one O-benzyl-oxime;
 20 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one O-allyl-oxime;
 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one oxime;
 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one O-*tert*-butyl-oxime;
 25 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one O-ethyl-oxime;
 (1S,3S,4S,8R)-5-Allyloxy-3-(3,4-dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decane;
 Ethyl (1S,3S,4S,8R)-2-[3-(3,4-dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]dec-5-yliden]acetate;
 30 (1S,3S,4S,8R)-3-(4-Chlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]decan-5-one oxime;
 N1-[1S,3S,4S,8R)-3-(4-Chlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]dec-5-yl]acetamide;
 (1S,3S,4S,8R)-3-(3,4-Dichlorophenyl)-7-azatricyclo[5.3.0.0^{4,8}]dec-5-yl amine;
 or a pharmaceutically acceptable addition salt thereof.

- 35 7. The use according to anyone of claims 1-5, wherein the disease to be treated, prevented or alleviated is an ischemic disease, an anoxic episode, or an injury to the brain and other parts of the CNS caused by trauma or other injury, such as a blow to the head.

8. The use according to anyone of claims 1-5, wherein the disease to be treated, prevented or alleviated is selected from an cerebrovascular disorder such as cerebral ischemia or cerebral infarction resulting from such as tromboembolic or haemorrhagic stroke, cerebral vasospasm, hypoglycaemia, cardiac arrest, perinatal asphyxia, anoxia such as from near-drowning, pulmonary surgery or cerebral trauma.

9. The use according to anyone of claims 1-5, wherein the disease to be treated, prevented or alleviated is selected from brain damage following or caused by: cerebral ischemia, cardiac arrest, high-risk surgery such as cardiac surgery, stroke, neonatal hypoxia, hypoxia caused by compromised lung function, neonatal anoxia, anoxia caused by compromised lung function, cerebral trauma, secondary regional ischemia induced by brain oedema, increased intercranial pressure, open brain surgery, endarterectomy, surgical interventions involving temporary, artificially sustained arrest of cardiopulmonary functions resulting in impairment of cerebral blood flow, or emergency treatment involving cardiopulmonary resuscitation (CPR).

10. A method for the treatment, prevention or alleviation of diseases associated with reduced blood flow to the brain or with an instance of a temporary break in blood supply to the brain in a subject, comprising administering to said subject a therapeutically effective amount of a tropane derivative having dopamine reuptake inhibitor activity or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00796

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/46 A61P9/10 A61P25/00 //C07D451/02,C07D471/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, WPI Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 064128 A (JAEAETTELAE MARJA ;LADEMANN ULRİK (DK); NEUROSEARCH AS (DK); PETER) 22 August 2002 (2002-08-22) claim 4, page 18, line 7, line 15-18, line 21-22, claim 5	1-10
X	US 4 179 567 A (CLARKE ROBERT L ET AL) 18 December 1979 (1979-12-18) the claims column 4, line 34 -column 5, line 29	1-10
X	US 5 272 160 A (CHENARD BERTRAND L) 21 December 1993 (1993-12-21) column 2, line 1-50 column 7, line 65 -column 8, line 68 column 19, line 43-65 column 20, line 22-24	1-10
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

20 February 2003

Date of mailing of the international search report

10. 03. 2003

Name and mailing address of the ISA

European Patent Office, P.B. 6818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

GERD STRANDELL/JA A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00796

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 06081 A (PFIZER ;CHENARD BERTRAND L (US); BUTLER TODD W (US)) 29 February 1996 (1996-02-29) page 38, line 8 -page 41, line 9 page 14, line 1-12; claims 1,15,20,23-25 ---	1-10
X	WO 01 28550 A (GLEICH GERALD J ;MAYO FOUNDATION (US)) 26 April 2001 (2001-04-26) page 6, line 1-3; claims 6,7,12 ---	1-10
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1998 XIAO-JUN ET AL: "Protection of neuronal uptake-1 inhibitors in ischemic and anoxic hearts by norepinephrine-dependent and -independent mechanisms " retrieved from STN INTERNATIONAL, FILE, accession no. 1998:645137 Database accession no. 130:329 XP002231942 & Journal of Cardiovascular Pharmacology (1998), 32(4), 621-628 abstract ---	1-10
Y	LEVIEL V: "The reverse transport of DA, what physiological significance?" NEUROCHEMISTRY INTERNATIONAL. ENGLAND FEB 2001, vol. 38, no. 2, February 2001 (2001-02), pages 83-106, XP002231900 ISSN: 0197-0186 page 95, right column, third paragraph - page 96, right column, second paragraph ---	1-10
Y	WO 97 16451 A (NEUROSEARCH AS ;SCHEEL KRUEGER JOERGEN (DK); OLSEN GUNNAR M (DK);) 9 May 1997 (1997-05-09) the whole document ---	1-10
Y	WO 97 30997 A (NEUROSEARCH AS ;SCHEEL KRUEGER JOERGEN (DK); MOLDT PETER (DK); WAE) 28 August 1997 (1997-08-28) the whole document ---	1-10
Y	WO 95 28401 A (MOLDT PETER ;WAETJEN FRANK (DK); NEUROSEARCH AS (DK); SCHEEL KRUEG) 26 October 1995 (1995-10-26) the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00796

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **10**
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: **1 in part**
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 10

Claim 10 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

Continuation of Box I.2

Claims Nos.: 1 in part

Present claim 1 relates to the use of any tropane derivative defined by reference to a desirable characteristic or property, namely having dopamine reuptake inhibitor activity. Claim 1 covers the use of all tropane derivatives having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for only a very limited number of such derivatives. In the present case, claim 1 so lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, claim 1 also lacks clarity (Article 6 PCT). An attempt is made to define the used tropane derivatives by reference to a result to be achieved. Furthermore, the wording "disease associated with reduced blood flow to the brain or with an instance of a temporary break in blood supply to the brain" is not clear and concise. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claim which appear to be clear, supported and disclosed, namely mainly those parts relating to use of the compounds according to claims 2-6 for the treatment, prevention or alleviation of the diseases defined in claims 7-9.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 02/00796

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02064128	A	22-08-2002	WO 02064128 A1	22-08-2002
			WO 02064139 A1	22-08-2002
US 4179567	A	18-12-1979	US 4214084 A	22-07-1980
US 5272160	A	21-12-1993	WO 9014087 A1	29-11-1990
			US 5338754 A	16-08-1994
			US 5391742 A	21-02-1995
			US 5710168 A	20-01-1998
			US 5527912 A	18-06-1996
			AT 150021 T	15-03-1997
			AU 618191 B2	12-12-1991
			AU 5512590 A	22-11-1990
			BR 1101053 A3	28-03-2000
			CA 2016860 A1	17-11-1990
			CN 1032209 B	03-07-1996
			CZ 9002328 A3	15-07-1998
			DD 294484 A5	02-10-1991
			DE 69030134 D1	17-04-1997
			DK 398578 T3	13-10-1997
			EP 0398578 A2	22-11-1990
			ES 2098248 T3	01-05-1997
			GR 3023314 T3	29-08-1997
			HK 1000468 A1	27-03-1998
			IL 94357 A	04-08-1996
			IL 114174 A	18-06-1996
			JP 2001886 C	20-12-1995
			JP 3005478 A	11-01-1991
			JP 7035368 B	19-04-1995
			KR 9204138 B1	25-05-1992
			NO 914485 A ,B,	15-11-1991
			NZ 233685 A	28-10-1992
			NZ 241346 A	28-10-1992
			PL 285190 A1	25-03-1991
			PT 94045 A ,B	08-01-1991
			SK 232890 A3	04-11-1998
			RU 2029769 C1	27-02-1995
			WO 9014088 A1	29-11-1990
			US 5185343 A	09-02-1993
			YU 95890 A1	28-05-1992
			ZA 9003741 A	24-12-1991
WO 9606081	A	29-02-1996	AU 684359 B2	11-12-1997
			AU 2351195 A	14-03-1996
			BR 9503694 A	28-05-1996
			CA 2197451 A1	29-02-1996
			CZ 9700474 A3	12-11-1997
			EP 0777652 A1	11-06-1997
			FI 970664 A	17-02-1997
			HU 77520 A2	28-05-1998
			WO 9606081 A1	29-02-1996
			IL 114892 A	16-07-2000
			JP 2888988 B2	10-05-1999
			JP 9509189 T	16-09-1997
			KR 224961 B1	15-10-1999
			NO 970728 A	17-02-1997
			NZ 284852 A	26-06-1998
			PL 318658 A1	07-07-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 02/00796

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9606081 A		RU 2139857 C1 TR 960451 A2 US 6046213 A	20-10-1999 21-07-1996 04-04-2000
WO 0128550 A	26-04-2001	AU 7847800 A WO 0128550 A1 US 6391888 B1	30-04-2001 26-04-2001 21-05-2002
WO 9716451 A	09-05-1997	AT 224392 T AU 702720 B2 AU 7563196 A BR 9611300 A CA 2236707 A1 CN 1201461 A ,B CZ 9801138 A3 DE 69623799 D1 DE 69623799 T2 EE 9800100 A WO 9716451 A1 EP 0858461 A1 HK 1016984 A1 HU 9802534 A2 IL 123898 A JP 11514638 T JP 3157839 B2 NO 981609 A NZ 321970 A PL 326448 A1 RU 2162469 C2 SK 42298 A3 TR 9800780 T2 US 5998405 A	15-10-2002 04-03-1999 22-05-1997 15-06-1999 09-05-1997 09-12-1998 15-07-1998 24-10-2002 30-01-2003 15-10-1998 09-05-1997 19-08-1998 20-07-2001 28-04-1999 08-08-2001 14-12-1999 16-04-2001 26-06-1998 28-02-2000 28-09-1998 27-01-2001 07-10-1998 21-07-1998 07-12-1999
WO 9730997 A	28-08-1997	AT 203023 T AU 720358 B2 AU 1794097 A BG 102637 A BR 9707636 A CA 2244773 A1 CN 1211982 A ,B CZ 9802520 A3 DE 69705608 D1 DE 69705608 T2 DK 885220 T3 EE 9800254 A WO 9730997 A1 EP 1130020 A1 EP 0885220 A1 GR 3036829 T3 HK 1018957 A1 HU 9901199 A2 IL 125146 A JP 3238414 B2 JP 2000504739 T NO 983877 A NZ 330886 A PL 328503 A1 PT 885220 T	15-07-2001 01-06-2000 10-09-1997 30-06-1999 27-07-1999 28-08-1997 24-03-1999 11-11-1998 16-08-2001 16-05-2002 15-10-2001 15-02-1999 28-08-1997 05-09-2001 23-12-1998 31-01-2002 27-09-2002 30-08-1999 10-03-2002 17-12-2001 18-04-2000 21-08-1998 25-02-1999 01-02-1999 30-11-2001

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 02/00796

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO 9730997	A	RU 2167876 C2 SI 885220 T1 SK 92998 A3 TR 9801641 T2 US 2002128284 A1 US 6288079 B1 US 2001018444 A1 ZA 9701525 A	27-05-2001 31-12-2001 04-11-1998 23-11-1998 12-09-2002 11-09-2001 30-08-2001 21-10-1997	
WO 9528401	A	26-10-1995	AT 222587 T AU 690257 B2 AU 2257595 A BG 63259 B1 BG 100883 A BR 9507489 A CA 2187309 A1 CN 1148854 A ,B CZ 9602982 A3 DE 69527839 D1 DE 69527839 T2 DK 756596 T3 EE 9600132 A WO 9528401 A1 EP 0756596 A1 FI 965074 A HU 75865 A2 JP 2899418 B2 JP 9505607 T KR 210417 B1 LV 11738 A LV 11738 B NO 964180 A NZ 284075 A PL 316876 A1 RU 2134264 C1 SK 128896 A3 US 5736556 A ZA 9508760 A	15-09-2002 23-04-1998 10-11-1995 31-07-2001 31-03-1998 12-08-1997 26-10-1995 30-04-1997 11-06-1997 26-09-2002 02-01-2003 23-12-2002 15-04-1997 26-10-1995 05-02-1997 17-12-1996 28-05-1997 02-06-1999 03-06-1997 15-07-1999 20-04-1997 20-12-1997 16-12-1996 26-01-1998 17-02-1997 10-08-1999 09-04-1997 07-04-1998 09-05-1996

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.